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THE MECHANISM OF PRODUCTION OF SUPPRESSION OF URINE IN BLACKWATER FEVER.

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SUPPRESSION of urine is a by no means infrequent sequel to an attack of blackwater fever, and owing to the extreme gravity of the symptom the mechanism of its production is a problem of considerable practical importance. The work of Werner¹ and of Barratt and Yorke² upon the condition obtaining in the kidneys of blackwater fever patients who have succumbed from suppression of urine has demonstrated the existence of granular material in the lumen of the renal tubules, and these authors infer that suppression of urine is of mechanical origin, dependent upon the occlusion of the tubules by granular plugs. On the other hand, a nervous inhibition of glomerular secretion is regarded by A. Plehn³ as the essential factor in the causation of this condition, and, again, nephritis has been mentioned by some authors as playing an important rôle in the production of suppression of urine.

Whether the occurrence of haemoglobin free in the blood plasma and its subsequent elimination by the kidneys is sufficient to produce suppression of urine through mechanical blocking of the renal tubules, or whether a nephritis, or nervous inhibition of glomerular secretion, is to be regarded as the essential factor in the development of this condition in blackwater fever is a question, therefore, which has not, as yet, been definitely decided. It was with the object of throwing further light upon this subject that these investigations were undertaken.

The first point to be determined was whether the presence of haemoglobin free in the blood plasma would under certain circumstances lead to suppression of urine in a normal animal.

With a view to investigating this question, an isotonic solution of haemoglobin was made as follows: Red blood cells obtained from rabbits were washed several times in normal

salt solution and then laked by the addition of distilled water, and the solution subsequently made isotonic with sodium chloride. A considerable precipitate of stromata appeared on the addition of the salt, and was thrown down by the aid of the centrifuge.

The clear solution of haemoglobin, warmed to 37° C., was slowly injected into one of the veins of the ear of a normal rabbit. In order to facilitate examination of the urine a cannula was tied into the bladder. The urine in the cannula was observed to be tinged with haemoglobin a few minutes after the injection.

Our earlier attempts to produce anuria by this means were invariably unsuccessful. Injection of the haemoglobin solution was followed by an increased flow of urine. This was probably to be explained by the diuretic action of the sodium chloride solution in which the haemoglobin was dissolved. After a time the diuresis subsided, but, as a rule, it lasted until the haemoglobinuria was distinctly decreasing in amount.

In later experiments we endeavoured to reproduce more closely the conditions obtaining in blackwater fever in man. In this disease the blood is anaemic, and the patient is more or less collapsed. It appears probable that a decreased filtering force in the glomeruli, resulting from a low blood pressure, may play a not unimportant part in the production of anuria in these cases.

With this consideration in view, it was decided to reduce the blood pressure of our experimental rabbits, partly by keeping the animals on as dry a diet as possible for twelve hours previous to the injection of haemoglobin, and also during the experiment, and partly by bleeding the animal to a moderate degree from the external jugular vein.

In order to obviate as far as possible the diuretic action of the sodium chloride, the strongest obtainable solution of haemoglobin was employed. Such solutions were prepared by dissolving the washed erythrocytes in the minimum quantity of distilled water necessary to produce complete laking. As a result of adopting these precautions we succeeded in producing suppression of urine in a number of animals.

Condition of the Urine after Injection of Haemoglobin Solution.

Although the first few specimens of urine passed after the intravenous injection of haemoglobin were clear, later samples were found to contain a quantity of solid material in suspension. In the earlier stages this consisted mostly of finely granular casts and débris. Later, however, the character of the deposit changed considerably. In addition to the granular material, large numbers of renal epithelial cells—isolated and also in the form of epithelial casts—were found. Both the free cells and also those of the casts were frequently loaded with fine brown granules. Occasionally, a complete cast of the epithelium lining a portion of a renal tubule was seen in the form of an epithelial cylinder filled with granular material. On a few

occasions red blood cells were found, and, rarely, well marked red cell casts.

If no marked degree of suppression supervened, the urine cleared up after a certain time, depending upon the amount of haemoglobin injected, and the deposit of granular material and epithelium gradually diminished, until finally the urine became normal. In several cases the flow of urine was greatly diminished, or ceased altogether for a period. In one experiment the animal developed complete anuria lasting over sixty hours; subsequently, the secretion of urine gradually became re-established. In such cases the urine was greatly altered. It was loaded with albumen, and on centrifugalization a heavy deposit was thrown down, consisting of granular casts, some of which were built up of granules of very large size ($3-4\ \mu$) and enormous numbers of more or less degenerated renal epithelial cells and casts. This condition persisted until the animal's death.

Condition of the Kidneys.

In the course of our experiments we had an opportunity of examining kidneys removed in all stages of the experiment, from shortly after injection of haemoglobin until complete suppression of urine had occurred. The kidneys removed a couple of hours after a single injection of haemoglobin were only slightly altered in appearance. They were of dark red or chocolate colour. Microscopically, a number of the convoluted tubules were seen to contain brownish-coloured plugs.

A much more striking feature was afforded, however, by those kidneys which were removed after several injections of haemoglobin. Here these organs were distinctly enlarged and heavier than those of normal rabbits. As before, they were of a dark chocolate colour. On section the cortex was found to be thicker than normal, and the whole kidney was seen to be traversed by dark lines, giving it a markedly striated appearance. Frequently these dark coloured streaks were grouped in fan-shaped areas, whilst the aspect of the intervening spaces was normal. The microscopical appearances presented by the kidneys were very characteristic.

A large number of the convoluted tubules and tubes of Henle were filled with plugs of granular material, and here and there epithelial cells were found intermingled with the granular casts. The casts extended down into the large collecting tubules of the papilla. No deposit was found in the meniscus of Bowman's capsules. Many of the convoluted tubules and tubes of Henle were distended and the epithelium in places had broken away from the basement membrane.

In the case of those animals in which suppression of urine has occurred the kidneys were profoundly changed. They were greatly increased in size and weight, sometimes weighing more than twice that of a normal rabbit.

Microscopical examination showed that the whole structure of the kidney was radically altered. The tubules of the cortex and subcortical region were enormously dilated, and many of

them contained casts of granular material and epithelium in various stages of degeneration. The epithelium lining the tubules was in many places exceedingly thin, and in others had completely disappeared.

Scattered here and there between these large dilated tubules were small islands of tubules tightly packed together, so that their lumina were completely obliterated. Some of the glomeruli were enormously distended, and others, like certain of the tubules, so crushed as to be scarcely recognizable. The large collecting tubules were also much involved. In many places the epithelial cells had broken away from the basement membrane and were either lying loose within the tubule or had entirely disappeared. In other tubules the epithelium was intact, but the lumina were filled with masses of epithelial cells and granular débris. Occasionally a collecting tubule was found in which the lining epithelium was normal and the lumen entirely filled by a mass of granular material and isolated epithelial cells surrounded by a ring of epithelium, evidently derived from a higher portion of the same collecting tubule.

If the information obtained from examination of the urine be considered in conjunction with that derived from a study of the pathological condition obtaining in the kidneys, one is able to form a fairly definite conception as to the effect which intravenous injection of haemoglobin has upon the renal secretion of an otherwise normal animal. The immediate result of such injections is a diuresis, dependent upon the action of the sodium chloride solution used for dissolving the haemoglobin. At the same time the renal epithelium commences to excrete haemoglobin into the tubules. At first this is quickly carried away by the rapid secretion of watery urine from the glomeruli. The result is a considerable flow of clear urine containing haemoglobin in solution. As the diuresis subsides the haemoglobin, or a closely related derivative, becomes deposited to a certain extent in the tubules. At this stage the urine is less in amount, and contains a quantity of solid material, consisting chiefly of granular casts and débris. Still later, especially when the degree of haemoglobinaemia is high, epithelial cells are shed from the lining membrane of the renal tubules. This is probably dependent upon one or both of the following factors. In the first place it is possible that the excretion of large quantities of a foreign substance like haemoglobin may be attended by injurious effects upon the renal epithelium. In the second place the presence of casts of lumen of the tubules would tend to damage the lining epithelium mechanically, either by friction as the plug was forced down the tubules owing to the *vis a tergo* of the glomerular secretion or by causing a complete or partial block of the tubule, and, as a result, dilatation of that portion above the plug, and, consequently, separation of the epithelium from the basement membrane.

This stage represents the commencement of the development of suppression of urine. Gradually, as haemoglobin continues to be excreted by the renal epithelium more and more tubules become occluded. The situation in which complete blocking of the lumen first occurs appears to be, as a rule, the narrow tubules of Henle. Coincidentally with the plugging of the tubules there is a marked diminution

in the amount of urine voided, and also of the haemoglobin it contains. The condition steadily progresses, until, finally, complete anuria results. After cessation of the flow of urine has lasted for a certain time a gradual re-establishment of urinary secretion occurs. The urine is loaded with albumen, and is exceedingly turbid. On centrifugalization a large deposit, sometimes equalling as much as one-fourth of the volume of urine, is thrown down. This deposit consists of granular casts, epithelial casts, granular débris, and degenerated epithelial cells. Urine of this nature continues to be passed until the animal's death. During the period of total or partial anuria marked changes occur in the kidney. Owing to the continued secretion of the glomeruli those portions of the tubules above the plugs become enormously distended with fluid. As a result, the epithelium lining these portions becomes extremely thin, and in places entirely disappears. The dilated tubules press upon adjacent tubules, so that on microscopic examination the latter appear of small size, and their lumina are completely obliterated.

After a time, owing to gradual disintegration of the casts plugging the tubes, the urine commences to escape into the ureter once more.

The serum proteins and red blood cells pass through the damaged epithelium and those portions of the tubules devoid of epithelial cells, with the result that the urine is loaded with albumen. Although the casts may be to a great extent washed away in the course of the next few days, yet the renal tubules remain dilated and the serum proteins continue to escape into the urine until the animal's death, which in these cases is probably due to uraemia.

Conclusions.

It is evident from these experiments that, under certain conditions, the mere passage of haemoglobin through the kidneys of a healthy animal is sufficient to cause suppression of urine owing to occlusion of the lumen of the renal tubules by plugs of granular material derived from the haemoglobin. The process is considerably facilitated by any factor which tends to lower the blood pressure of the animal and, as a result, the secretion of water by the Malpighian capsules. On the contrary, when the blood volume is sustained by the injection of saline solution and by feeding the animal on moist food, a large amount of haemoglobin (41 grams) may be injected without any tendency to suppression of urine. It appears that these observations have an important bearing upon the treatment of suppression of urine in blackwater fever in man. On the earliest sign of any diminution in the volume of urine voided radical measures must be adopted. The patient should be given large quantities of fluid, by the mouth, if possible, or rectum, and cardiac stimulants, such as digitalis and caffeine administered. Should these not produce a copious flow of urine, recourse ought at once to be had to large intravenous injections of normal saline

solution. Our experiments indicate that it is useless delaying the adoption of these measures until suppression of urine has actually commenced. At this stage it is highly improbable that any procedure will be adequate to displace the casts. This is in agreement with the clinical observation that late intravenous saline injections usually fail to relieve suppression. When suppression has once developed and continued even for a short period the injury done to the kidneys is such that the result must of necessity be almost invariably fatal.

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- ¹ Ueber die Nieren beim Schwarzwasserfieber, *Archiv für Schiffs- und Tropenhygiene*, 1907, Band xi, Beiheft 6. ² An Investigation into the Mechanism of Production of Blackwater, *Annals of Tropical Medicine and Parasitology*, 1909, vol. iii, No. 1. ³ Die Nieren beim Schwarzwasserfieber, *Archiv für Schiffs- und Tropenhygiene*, 1903, S. 270.